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Original Article

Year-to-year changes in lung function in individuals with cystic fibrosis

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Abstract

Background: We examined the year-to-year change in FEV_1 for individuals and the overall cystic fibrosis population to better understand how individual trends may differ from population trends.
Methods: We calculated individual yearly changes using the largest annual FEV_1 percent predicted (FEV_1%) measurement in 20,644 patients (6–45 years old) included in the Epidemiologic Study of Cystic Fibrosis. We calculated yearly population changes using age-specific medians.
Results: FEV_1% predicted decreased 1–3 points per year for individuals, with maximal decreases in 14–15 year olds. Population changes agreed with individual changes up to age 15; however after age 30, yearly population change approximated zero while individual FEV_1% predicted decreases were 1–2 points per year.
Conclusions: Adolescents have the greatest FEV_1% predicted decreases; however, loss of FEV_1 is a persistent risk in 6–45 year old CF patients. Recognizing individual year-to-year changes may improve patient-specific care and may suggest new methods for measuring program quality.

Keywords: Cystic fibrosis; Pulmonary function; Annual trends

1. Introduction

Forced expiratory volume in 1 s (FEV_1) is the most important single factor predictive of survival in cystic fibrosis (CF) [1–5]. FEV_1 has a major impact on clinical decision making and serves as a critical endpoint for studies to improve outcomes with CF [6]. Declines in FEV_1 have been found to be predictive of increased hospitalizations and death in patients with chronic obstructive pulmonary disease [7,8]. In CF, the predictive ability of rates of decline in FEV_1 for death have been hypothesized and some evidence found for poorer outcomes with more rapid rates of decline [9–11], but several recent large studies of CF have failed to confirm such an association [2,3,12,13], and the finding can be elusive in other pulmonary diseases [14,15]. Nevertheless, more rapid rates of decline are found to be important in understanding disease for other clinical outcomes in CF as well as in other lung diseases [16–20].

Cross-sectional measurements of FEV_1 are a common basis for understanding FEV_1 trends over time [21], and clinicians are encouraged to use these trends to understand prognosis and plan therapy. Patients and their families are invited to review lung function trends as a measure of the quality of care provided in each certified CF Care Center in the United States [22]. However, aggregated population results for lung function decline may be

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misleading when attempting to understand individual outcomes [23–25], especially when derived from cross-sectional data [23,25–27], and individual assessments of lung disease progression may provide information not detectable in aggregated analyses [26,27].

We analyzed data from the Epidemiologic Study of Cystic Fibrosis (ESCF) [16] to discover if there are particular age groups that are prone to more rapid falls in FEV_1 percent predicted (FEV_1%). The ESCF data provide a uniquely precise record of frequent lung function measurements that are required for a study of individual decline in lung function [23,25,26]. Using this data, we examined FEV_1% from one selected year of age to the next year of age both in individuals and in the population to understand how individual experiences may differ from population experience [23,26,27] in the setting of CF. Knowledge of likely, individual outcomes from one year of age to the next may enable physicians to improve and tailor the intensity and nature of treatments to individuals to optimize therapy, minimize treatment burden and improve outcomes.

2. Methods

The data were obtained from ESCF, an encounter-based, longitudinal, multi-center study designed to understand the natural history of patients with CF in North America [16]. Written informed consent was obtained according to the policies governing research at each participating institution. Data were collected from 1994 to 2005. Baseline information such as birth date, sex, and race/ethnicity were recorded when the patient enrolled in the study. Pulmonary function test (PFT) results, height, weight, and the date of each exam were recorded in a prospective manner for each patient visit.

Age at the time of PFT was calculated as of the patient's last birthday, and FEV_1 measurements were included in this analysis for patient ages 6 through 45. We excluded measurements before age 6 because of a lack of standardized PFT methods and after age 45 because of insufficient data. We defined FEV_1% for a patient's year of age as the largest value during the year in which the patient had three or more FEV_1% values (for example, the largest value among the three or more measurements performed while the patient was age 8). We chose the best FEV_1% as being most reflective of the patient's true baseline lung function, and we required at least three values during the year in order to further reduce the likelihood of using atypically low values to represent that patient's lung function at that age. For consecutive years that a patient had this single largest FEV_1% value available, the year-to-year change between consecutive ages was calculated (e.g., the change from age 8 to age 9 was calculated using the single largest FEV_1% during each year of age).

The United States Cystic Fibrosis Foundation (CFF) Patient Registry algorithm was used to determine FEV_1% [21]. Specifically, the Wang et al. method [28] was used for females through the age of 15 years and the Hankinson et al. method [29] was used for females aged ≥16 years. For males, the Wang et al. method was used through the age of 17 years and Hankinson et al. method for ages ≥18 years. Use of different normalization equations for measurements taken at different time points could introduce artifact into our analysis. Thus, we performed sensitivity analyses and confirmed that using different calculation methods [28–30] had an effect on the FEV_1% changes during mid-adolescence, an age period of particular interest. Because of this finding, additional sensitivity analyses of changes in FEV_1% from one age to the next were calculated using only one method within each sex (Table 1).

All eligible FEV_1% values (as described above) were included to calculate the population mean, median, and distribution of FEV_1% for each age from 6 to 45. From these data, the year-to-year changes in the population median FEV_1% were determined. In addition, the mean, median and distribution of year-to-year individual changes in FEV_1% were calculated. These individual changes were also characterized by the percent of patients with an absolute decrease in FEV_1% of ≥5 points and ≥10 points.

The impact of several assumptions was explored using sensitivity analyses. First, we relaxed the criterion of requiring three FEV_1% measurements during an age year to requiring only one measurement to examine potential bias related to frequency of patient monitoring. Second, we examined the potential for bias in year-to-year individual changes due to censoring (loss to follow-up, lung transplantation, or death) immediately after two consecutive FEV_1% measurements by examining the effect of restricting calculations to patients with a minimum of two additional years of data beyond the pair of years evaluated.

3. Results

This analysis included 20,664 patients contributing at least 1 year of data for calculation of aggregated measures of FEV_1%, with 4013 patients at 6 years old, a high of 5103 patients at 11 years old, and a steady decrease in patient numbers to 175 patients at 45 years old (data shown as vertical bars in Fig. 1). For the analyses of individual year-to-year changes, there were 2816 patients with data for consecutive ages 6 to 7, a high of 3645 patients with data for ages 10 to 11, and 118 patients for ages 44 to 45. Age pairs older than 45 had fewer than 100 patients, so they were not included in this analysis.

Summary statistics of the aggregated population data show that after an initial period of modest decline in FEV_1%, there is a steeper decline from early adolescence to early adulthood

Table 1
Methods for calculating change in FEV_1% from one age to the next*.

Method		Ages				
		14 to 15 (and prior)	15 to 16	16 to 17	17 to 18	18–19 (and later)
CFF algorithm	Females	W–W	W–H	H–H	H–H	H–H
	Males	W–W	W–W	W–W	W–H	H–H
Current analysis	Females	W–W	W–W	H–H	H–H	H–H
	Males	W–W	W–W	W–W	H–H	H–H

*CFF = Cystic Fibrosis Foundation [3]; W = Wang, et al. Method [7]; H = Hankinson, et al. method [8].

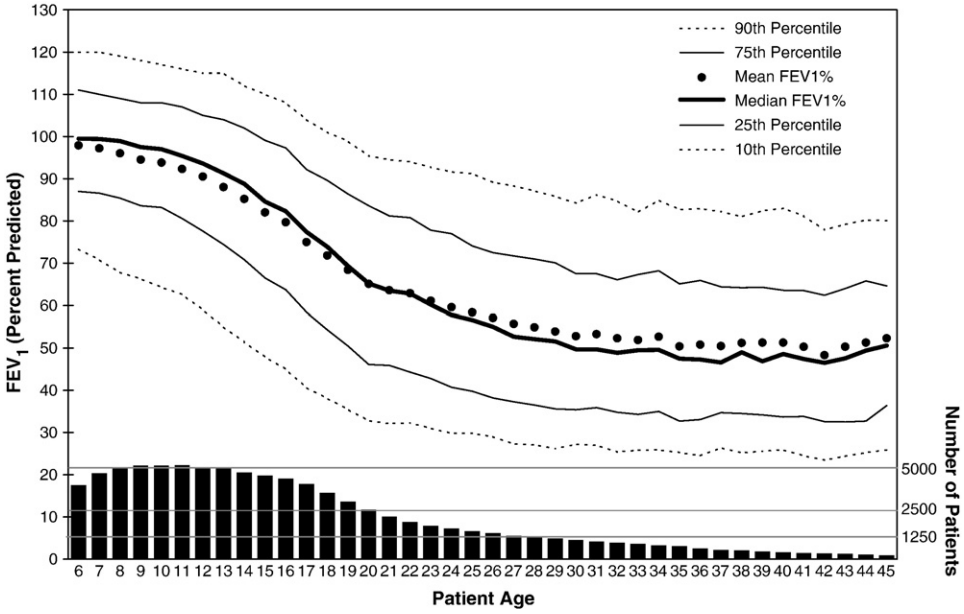

Fig. 1. Population FEV_1 percent predicted by age. The largest FEV_1% value for each year of age is shown in aggregated form. Data for patients included in the data base for multiple years are included in the calculations for every year of age available. FEV_1 was normalized to percent predicted values calculated using methods of Wang, et al. [28] and Hankinson, et al. [29] in accordance with CF Foundation Registry convention [21]. The bold line shows the median population value at each age, while circles represent the mean at each age. To provide a sense of the variation seen within the population for each year of age, lighter solid lines show the 25th and 75th percentiles, and dotted lines show the 10th and 90th percentiles. The number of patients contributing data for each year of age is shown by the superimposed bar chart at the bottom of the graph (right axis).

followed by another period of modest decline to about age 30, after which the FEV_1% appears relatively stable (Fig. 1).

Examination of FEV_1% values for consecutive years of age reveals that for most ages the individual year-to-year change is a drop of 1 to 3 FEV_1% points (Fig. 2a). The mean and median of individual year-to-year changes are always negative, with progressively worse declines until about age 15 and smaller declines through adulthood to age 45. Through age 15, the change in median FEV_1% based on aggregated population data agrees well with individual data for year-to-year change (Fig. 2b). In contrast, the change in median FEV_1% based on the population data shows higher variability after age 15, but it approximates zero in patients over age 30.

A substantial fraction of patients have relatively large individual year-to-year drops in FEV_1% (Fig. 3). For every age pair from 6 to 7 through 41 to 42, over 20% of patients have decreases of ≥ 5 FEV_1% points. At the peak age of 15 to 16, this approaches 50% of patients. For each age pair from 6 to 7 through 26 to 27, over 10% of patients have drops of ≥ 10 FEV_1% points, again peaking at ages 15 to 16, when almost 25% of patients have a decrease this large. This mirrors the results of year-to-year drops in median FEV_1% shown in Fig. 2a.

All of our results were stable through sensitivity analyses designed to detect bias introduced by non-uniform numbers of repeated measurements each year, by the effects of differing methods of FEV_1% calculation, and by the effects of early censoring from the study due to loss to follow-up, lung transplantation, or death. Repeated analyses after splitting the data set into two cohorts, 1994–1999 and 2000–2005 showed no secular trends. Stratification of the data by gender revealed very similar behavior in year-to-year changes in lung function. Using CF Foundation methods to normalize lung function revealed that male patients had their greatest drop in lung function in the age 14–15 cohort while females had their greatest drop in the age 15–16 cohort. Using Stanojevic normalization equations, both males and females had their maximal year-to-year changes in the age 19–20 cohort.

4. Discussion

A population-based view of FEV_1 in CF is helpful for understanding the impact of therapy on a population and is useful for assessing quality improvement [21,22,31]. This study demonstrates the importance of considering individual patient experiences with year-to-year change in FEV_1% in addition to the aggregated population experience. Our population results (Fig. 1) are consistent with previously published observations [21]. However, we show that individual trends in FEV_1% year-to-year differ from the cross-sectional population trends and that individuals can have enormous variance from cross-sectional trends. The fact that cross-sectional results do not always accurately represent longitudinal changes in pulmonary function has been previously observed in healthy male adults [23], and the issue has been considered in a number of subsequent studies in various pulmonary diseases [8,11,14,15,17–20,26,27,32]. Such differences between individuals and the overall population may change assessments of individual prognosis and the nature and intensity of patient-specific treatment plans. Most importantly for clinical practice, knowledge of likely near-term lung function trajectory allows optimization of therapy on an individual basis,

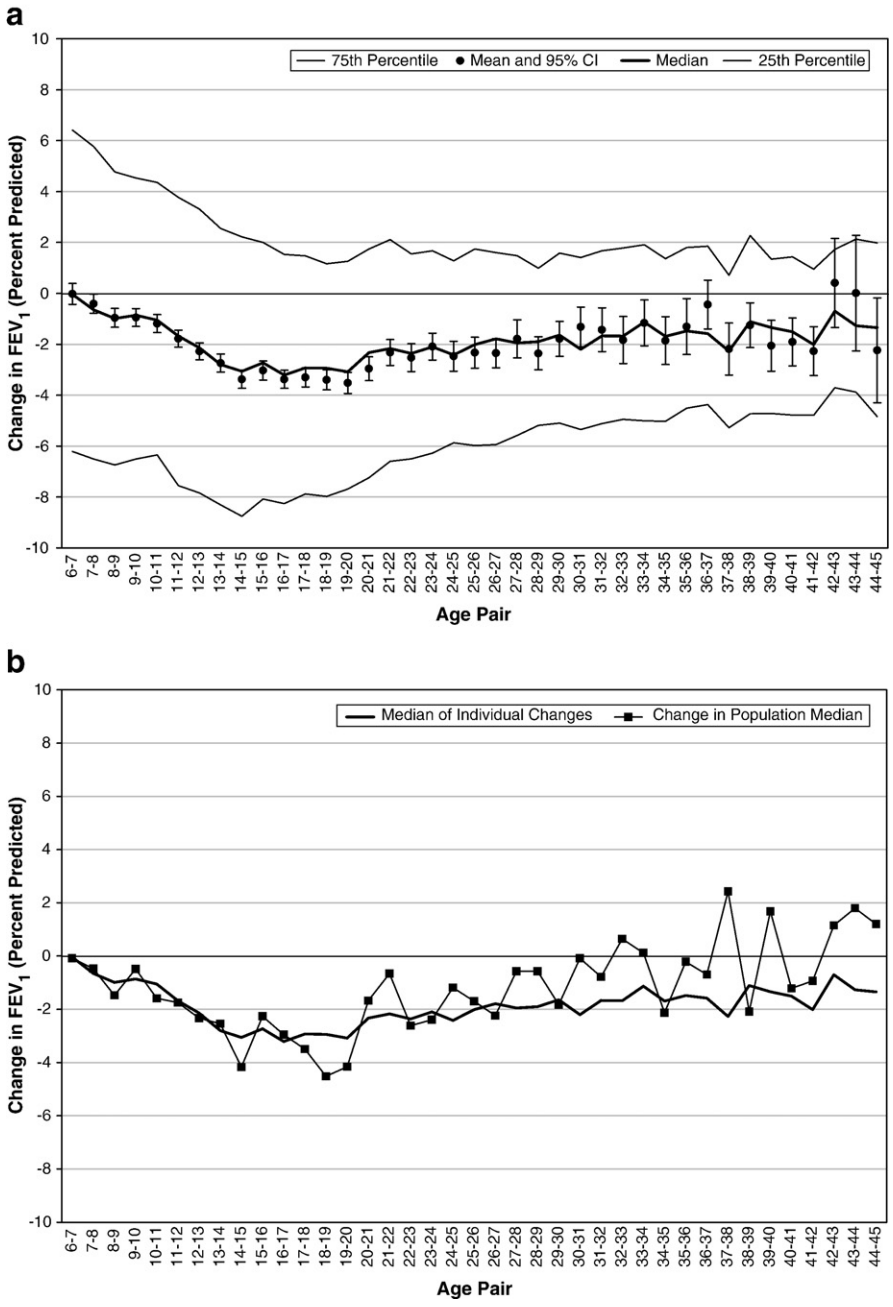

Fig. 2. a. Individual changes in FEV_1 percent predicted by age. FEV_1%s at each age were calculated using modified methods of Wang, et al. [28] and Hankinson, et al. [29] (see methods in text and Table 1). The bold line shows the median of the individual year-to-year changes for each age group, while solid circles with bars represent the mean and 95% confidence interval at each age. The lighter curves represent the 25th and 75th percentiles and provide a sense of the variance for each age group. b. Median of individual changes in FEV_1% and change in population median of FEV_1% by age. A curve with squares and a light line showing the change in the population median FEV_1% from year-to-year is superimposed on the median of *individual* year-to-year changes at each age (bold curve). The population aggregate year-to-year changes parallel individual changes through early adulthood. However following approximately age 30, the aggregated population changes are more optimistic than observed for individuals (see text for further discussion).

especially for those patients with high variance in trajectory from the aggregated trajectory and provides additional incentive for patients and their caretakers to adhere to often burdensome therapies.

The data indicate that adolescents are at higher risk of decreases in lung function than younger patients or adults. The propensity to lose lung function year-to-year increased progressively from age 6 to age 15. Others have found FEV_1% in mid-adolescence to be of particular importance in predicting survival with CF [3], increasing the level of concern over adolescent year-to-year lung function losses. Adolescents had twice the median year-to-year loss in lung function as adults and thus had the highest likelihood of large drops in lung function (Fig. 3). Our sensitivity analyses show that this is unlikely to be due to survivor bias and highlights the need to better understand the challenges posed by the combination of adolescence and CF and, perhaps

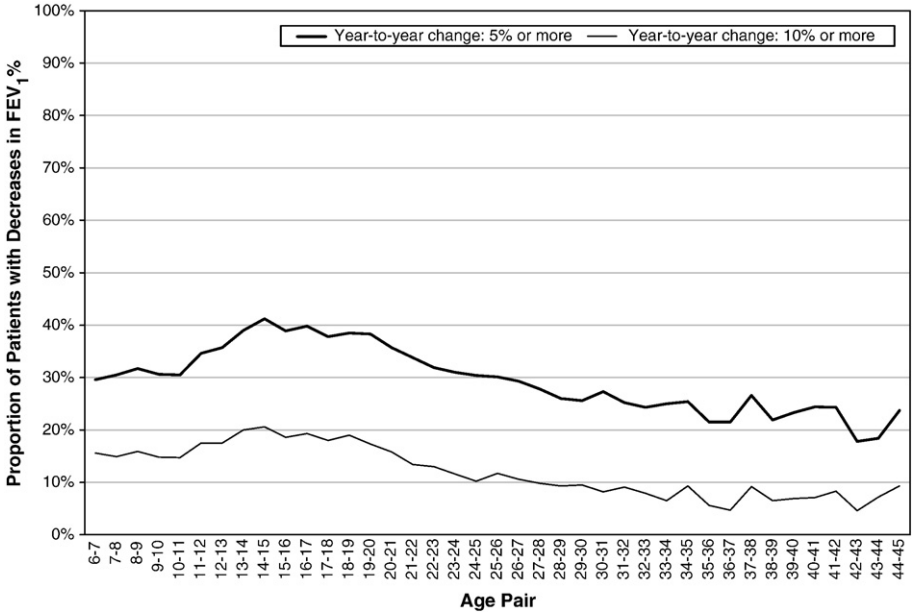

Fig. 3. Large decreases in FEV_1% by age. The individual year-to-year changes in FEV_1% at each age were calculated as described in the text and Table 1. The bold curve shows the percent of patients with a decrease of 5% or more in FEV_1% during a single year-to-year age group. The lighter curve reveals the percentage of patients with decreases of 10% or more in FEV_1%. Regardless of age group, substantial numbers of individual patients with CF suffer large drops in FEV_1% (see text for further discussion).

more importantly, why progressively larger decreases in lung function begin around ages 9 to 11 and continue through adolescence (Fig. 2, panels a and b).

Although patients who reach adulthood have a decreased tendency to lose FEV_1%, the median loss remains nearly 2 percentage points per year through middle adulthood (Fig. 2, panel a). This effect sharply contrasts with results from the analysis of aggregated population data (Fig. **2**, panel b) that show that median FEV_1% change fluctuates and approximates zero among adults. This contrast may potentially give clinicians a false sense of security when considering the presumed future clinical course of older patients with CF, while simultaneously discouraging both physicians and patients when an individual year-to-year change is observed to be negative. The loss of lung function may incorrectly suggest that a patient has failed to fight CF effectively enough to meet population-based expectations.

Among older patients with CF, survivor bias influences the cross-sectional population measurement of FEV_1. Death and lung transplantation tend to remove patients with low lung function from the population, thus minimizing the size of year-to-year decrease in aggregated mean and median FEV_1%. However, this analysis explicitly conditions the calculation of *individual* year-to-year change on those who survived to the second year, thus providing an estimate of the tendency to lose function among patients who survive to need further care (which is the majority of patients for any age year in our study).

The positive emphasis on improving quality of care at CF centers is currently guided by population statistics [21]. Improvements that preserve average lung function within a center should improve individual lung function. However, considering only nationally derived aggregated population data may obscure the importance of individual year-to-year changes, especially among adult patients with CF. Within a specific CF care center, there may be greater differences between center statistics and individual patient statistics due to generally increased variability in smaller groups. The addition or subtraction of a single patient can substantially influence the population results for a small group. Thus, care centers should use population statistics to understand center-specific trends with regard to quality improvement but should also carefully observe the outcomes of interventions to improve lung function for individual patients from year to year. Identification of those patients with the greatest declines in lung function from one year to the next may pinpoint those most in need of additional attention.

The stability of the year-to-year changes in individuals, as assessed by the sensitivity analyses performed, strongly suggests that survivor bias (e.g., loss to follow-up, lung transplantation, death), non-uniform data collection, and different methods of FEV_1% calculation are not the source of our findings. However, other biases that we could not detect could have influenced our results. Our study results varied somewhat when different equation sets [21,28–30] were employed for normalization of lung function. However, regardless of equation set, we found consistently high rates of decline among adolescents and persistence of decline throughout our adult study population. Our study was not much affected by varying normalization equations for lung function but rather uncovered and high-lighted potential artifacts that may exist in the understanding of lung function decline based on cross-sectional studies that use different equations at different ages. High FEV_1% is an independent predictor of more rapid decline in lung function, and that may have contributed, in part, to the effect that we observed in children and adolescents aged 6 to

17 years [33]. However, this effect is insufficient to explain differences between aggregated and individual year-to-year changes in lung function, especially among adults. We did not evaluate the effects of treatment because these often depend on FEV_1%, the object of our study thus representing a potential confounder to avoid. Nor did we evaluate outcomes other than FEV_1% for year-to-year changes because our goal was to better understand and reflect the emphasis placed on FEV_1% within the CF community and the literature on CF [1,2,5,21,33]. Because our study was limited to patient ages 6 through 45, we cannot comment on year-to-year changes for the very young or the growing number of adults older than 45 with CF. Finally, because of rapid and welcome advances in care for CF patients, we cannot predict whether the adolescents that we studied will eventually exhibit the same pattern of year-to-year changes that we saw among the adults that we studied.

Cross-sectional observations of year-to-year change in lung function are helpful for understanding the impact of therapy on the aggregated population. We found, however, that individual year-to-year changes can differ, sometimes dramatically, from national and local aggregated changes in lung function. These observations regarding year-to-year individual trends in lung function for a wide range of patient ages provide information relevant to decision making in clinical practice especially to adapt to individual patient needs.

Conflict of interest statement

Theodore Liou, Michael Konstan, Wayne Morgan, and Jeffrey Wagener have received honoraria to attend meetings as members of the North American Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis (ESCF). Theodore Liou has received funding from the NIH/NHLBI, the CF Foundation and the Ben B. and Ira M. Margolis Family Foundation of Utah for work related to CF. He is a member of the CF Foundation Patient Registry Data Use Committee and is a steering committee consultant on the REVEAL registry project on PAH sponsored by Actelion. As the principle investigator for the Therapeutic Development Network Center at the University of Utah, Dr. Liou has received funding to participate in trials of novel treatments for CF from Altus, Axcan-Scandipharm, Bayer, Boehringer, Genentech, Gilead, Inspire, Kalobios, MPEX, Novartis and Vertex. Dr. Liou has consulted for the Gehrson Lehman Group. Eric Elkin and David Pasta are employees of ICON Clinical Research, Inc., which was paid by Genentech to provide biostatistical and analytic services. Joan Jacobs is an employee of Genentech, Inc. Michael Konstan has received payment from Genentech, Inc., for serving as Co-Chair of the North American Scientific Advisory Group and as a consultant. Wayne Morgan has received payment from the Cystic Fibrosis Foundation for serving as Chair of the Cystic Fibrosis Data Safety Monitoring Board and from Genentech, Inc., for serving as Chair of the North American Scientific Advisory Group, and is the recipient of research grant support from Novartis for a study being conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Inner City Asthma Consortium. Jeffrey Wagener was employed by Genentech until 2007, has done consultant work for Genentech and Gilead, is on advisory boards for Genentech and Gilead, and has received speaking honoraria from Genentech, Gilead, Roche, and Novartis during the last 3 years.

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